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<p>(51) International Patent Classification ⁵ : A61K 9/16</p>	<p>A1</p>	<p>(11) International Publication Number: WO 93/07859 (43) International Publication Date: 29 April 1993 (29.04.93)</p>
<p>(21) International Application Number: PCT/US92/08160 (22) International Filing Date: 24 September 1992 (24.09.92) (30) Priority data: 780,603 23 October 1991 (23.10.91) US (71) Applicant: WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventors: GHEBRE-SELLASSIE, Isaac ; 21 Meadow Bluff Road, Morris Plains, NJ 07950 (US). NESBITT, Russell, U. ; 292 Miller Avenue, Somerville, NJ 08876 (US). FAWZI, Mahdi, B. ; 11 Timberline Drive, Flan- ders, NJ 07836 (US).</p>		<p>(74) Agents: BULLITT, Richard, S. et al.; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US). (81) Designated States: CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE). Published <i>With international search report.</i></p>
<p>(54) Title: NOVEL PHARMACEUTICAL PELLETS AND PROCESS FOR THEIR PRODUCTION (57) Abstract Drug loaded pellets are produced through melt spheronization in which the active pharmaceutical is blended with various excipients and binders. The formulation is fed to an extruder where it is heated and extruded at a speed of approximately .05 to 10 mm/sec. at approximately 60-180 °C. The extrudate is then cut into pieces in a pelletizer and subsequently fed to a spheronizer for uniform pellet formulation. The pellets may be further coated so as to provide immediate, enteric or modified release characteristics.</p>		

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Novel Pharmaceutical Pellets
and Process For Their Production

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Background of the Invention

The present invention relates to a novel pelletization process whereby an active ingredient and appropriate excipients are blended and formed into spherical particles. Drug-loaded pellets are presently manufactured for the most part, by the application of a solution, suspension or powder of the active ingredient and excipients onto non-pareil seeds, or by sequentially blending, wet-granulating, extruding and spheronizing the active and excipients into pellets. Spheronization, which was introduced in Japan in the early 1960s, is a multi-step process that is employed mainly when pellets with very high drug loading capacities are needed to accommodate high dose products.

Solution/suspension layering is generally utilized only when pellets with a low drug loading capability are desired; for high drug loading, the processing times tend to be too long. The layering process is relatively simple and utilizes any conventional coating equipment, although fluid bed machines, due to their high drying efficiency, are the equipment of choice. Powder layering, probably the oldest pharmaceutical pelletization process, utilizes pieces of equipment that range from conventional coating pans to highly specialized centrifugal fluid bed equipment. In this process, the powder is layered on starter seeds with the simultaneous application of a binder solution. All three processes use organic solvents which are toxic and expensive or aqueous vehicles to produce the final

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pelletized product.

United States Patent No. 4,880,585 to Klimesch et al
discloses a continuous method of tableting extrudable
5 pharmaceutical mixtures whereby the mixture is extruded
and while still deformable is pressed between two rollers
that are driven in opposite directions. The rollers are
characterized by depressions on their surface that are
opposite one another, the form of these depressions
10 thereby determining the tablet shape. The pharmaceutical
mixture is comprised of the active agent and N-
vinylpyrrolid-2-one (NVP) polymer which is extruded to
form a melt. The polymer is incorporated into the
formulation so as to render it hydrophilic for
15 dissolution in the oral cavity.

U.S. Patent No. 4,801,460 to Goertz et al. discloses
a process for the preparation of pharmaceutical tablets
in which an active agent is mixed with N-vinylpyrrolid-2-
20 one polymer as a binder prior to melt extrusion or
injection molding. The NVP polymer is treated or
prepared with organic solvents or by using organic
peroxide as an initiator in aqueous solution. The
polymer binder must then soften or melt between 50° and
25 180°C so that the melt can be extruded and shaped into
tablets. The process allegedly allows rapid release
dosage forms to be produced in a wide variety of shapes
and sizes.

30 United States Patent U.S. No. 4,097,212 to Morishima
et al. discloses a granulator with a water-immersed
cutter with a casing attached at right angles to the end
of an extruder. The central circular wall of the casing
forms one mould surface and has an annular flow passage.
35 A number of radial nozzles are bored into the inner wall
and a central rotating cutter has a number of radial
blades with a specific gap between their outer layers and

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the inside molding face of the casing. The moulding wall is relatively thin resulting in a low flow resistance which allegedly produces uniform sized quality granules.

5 The use of hot melt screw extrusion to obtain sustained release pellets of freely soluble drugs in hard gelatin capsules is also discussed in an article published during a symposium for the Controlled Release Society. Follonier et al., Proceed. Intern. Syrup
10 Control. Rel. Boact. Mater 18 (1991.) There, diltiazem HCl, a calcium-channel blocking agent was extruded with several inert polymers as well as some pore forming agents for faster release rates.

15 Although not pharmaceutically related, PCT application No. PCT/U.S.88/02398 to Tsau discloses the use of a spheronizer to compact the dendritic crystals of the high intensity sweetener aspartame (APM) into dense,
20 non-porous granules of substantially spherical shape within a narrow particle size range. The granules are preferably further coated with a hydrophobic material such as fats, starches and proteins and the aspartame is thereby allegedly stabilized against heat, moisture and chemical degradation that would otherwise occur during
25 baking.

 The present invention does away with the need for water or organic solvents and provides particles that fall within a narrow particle size range. As a result,
30 water sensitive drugs and materials can also be employed without running the risk that the drug will be affected by the presence of the solvent. The removal of the organic solvents phase of the process that was required by the teachings of the prior art makes the
35 pharmaceutical dosage form less hazardous to manufacture and less toxic to the environment. The pellet cores may be further coated with materials such as sugars,

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polymers, waxes and the like. The coatings of the present invention may also be tailored to the particular need for drug delivery and may be designed to produce immediate, enteric or modified release products.

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Summary of the Invention

The present invention concerns a novel method for producing drug loaded pellets through melt
10 spheronization. The active pharmaceutical agent is blended with the necessary excipients and is then extruded under appropriate melting temperatures. The extrudate is then cut and the cylindrical segments spheronized to yield substantially uniform, equal-sized
15 pellets which may have immediate or modified release properties depending on the active, the added excipients and any further coatings which may be applied. No solvents, aqueous or organic, are required in the blending of the materials or during the hot melt
20 extrusion and spheronization. The process is continuous rather than a batch process, although the latter is also an option.

Detailed Description of the Invention

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The novel pelletization process of the present invention affords numerous advantages over those of the prior art. The process not only obviates the need for the use of hazardous organic solvents to blend the active
30 agent with the excipients in the pellet core formulations but also does away with the use of aqueous media in lieu thereof in the formulation during processing and thereby makes the process particularly suitable for a wide variety of water sensitive bio-active agents.

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Pharmaceuticals that may be pelletized according to the process of the present invention are numerous and

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varied. Suitable classes of bio-active agents include analgesics, anti-inflammatory agents, antibiotics, anti-depressants, anti-epileptics, antihypertensive agents, neuroleptics, corticosteroids, lipid regulating agents, antacids, laxatives, anti-ulcer agents, anti-arrhythmic agents, etc., and their combinations. The active ingredient is first blended with appropriate excipients in an appropriate mixer at a suitable speed until a homogeneous blend is obtained. For example, mixers such as planetary and high intensity mixers are useful in thoroughly mixing the active and the excipients. Suitable excipients include all water soluble and insoluble polymers such as cellulose derivatives, starches and their derivatives, polyvinyl pyrrolidone (PVP), acrylic polymers, and waxes as well as inorganic additives such as calcium phosphate, calcium sulfate, talc, aluminum silicate, etc. Surfactants, lubricants and other liquid excipients may be added to the formulation directly or from an aqueous or alcoholic medium.

The active pharmaceutical-excipient mixture is blended in active/excipient ratios of from about 1:100 to about 100:1 on a weight percentage basis. Preferably, the ratio is from about 1:10 to about 10:1 but is governed by the type of pharmaceutical employed, its dosage, etc.

The mixture is then transferred to an extruder such as a Brabender Twin Screw Extruder, C. W. Brabender Instruments Inc., S. Hackensack, New Jersey which has one or more heating zones. The mixture is extruded at appropriate melting temperatures which again are governed by the type of pharmaceutical and excipients that make up the formulation. The extrusion is run at temperatures that are of a degree sufficient to melt one or more of the ingredients so as to form a congealed mass of product

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as the mass exits the die attached to the end of the extruder. Generally, these temperatures may range from approximately 30°C to about 250°C and preferably from about 60°C to about 180°C.

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The extrudate is then fed either directly or through a conveyer belt into a pelletizer such as a Brabender pelletizer where they are cut into uniform cylindrical segments. The length of the segments depends upon the dimensions of the pelletizer knives, and generally may range in length from approximately 1.0 mm. to about 4.0 mm. The width of the extrudates is determined by the nozzle size and the rate at which the conveyor belt feeds the extrudates into the pelletizer. Preferably, the size of the nozzle opening employed should range from approximately 0.6 mm. to about 4.0 mm. in diameter while the rate at which the extrudates are fed into the pelletizer may range from approximately 0.05 mm./sec to about 100 mm./sec and preferably 0.05 to 50 mm./sec.

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The cylindrical segments are transferred into a spheronizer, for example, a Luwa Jacketed spheronizer, Luwa Corp. Charlotte, N.C. and spheronized at suitable speeds using appropriate temperatures. The jacketed spheronizer consists of a revolving plate or base confined within a wine-glass or goblet-shaped pot or container. The base may be smooth, grooved or ridged and by revolving at high speeds forces the extrudate segments to rapidly bounce and tumble about the confines of the spheronizer colliding with the walls and against one another. This motion compacts each piece as well as rounding its ends to a more spherical shape. The speed of the spheronizer may range from approximately 500 to about 5000 rev./min while the temperatures may vary from approximately 30°C to about 200°C and preferably 60°C to about 150°C. If necessary, the formed pellets are transferred into a cooled second chamber of the same

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spheronizer, or a second spheronizer fitted with a cooling jacket. Sometimes anti-adherents may be sprinkled onto the forming pellets to minimize tackiness. Suitable anti-adherents are selected from the group consisting of talc, calcium carbonate, magnesium tri-silicate, kaolin, etc., and mixtures thereof and serve to prevent the exudate pieces from sticking together during spheronization. The pellets are generally uniform in size and may vary from approximately 0.5 mm. to about 4.0 mm. in diameter depending of course, on the dosage of the pharmaceutical desired.

The pellets are then sieved and collected into containers for further processing. Since the active ingredient is dispersed throughout the matrix, the pellets generated may have immediate or modified release properties depending upon the physicochemical properties of the formulation components. Because the matrix which controls the rate of drug release is somewhat deformable, the pellets can be compressed into tablets without significant changes in release profiles.

If desired, the pellets may also be coated with appropriate coating materials to produce immediate, enteric or modified release products. Any conventional coating apparatus such as a fluid bed apparatus, centrifugal granulators and coating pans, etc. may be utilized to apply these coatings. For immediate release characteristics, suitable coatings include hydroxypropylmethyl cellulose, polyvinyl pyrrolidone (PVP), hydroxypropylcellulose and the like and may be applied in pellet/coating weight ratios of from about 20:01 to about 20:10. For enteric release, coatings such as cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), methacrylic acid copolymer, cellulose acetate trimellate and mixtures thereof may be used to coat the pellets in cut ratios of from about 20:1 to

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about 2:1. Suitable coatings for modified release (stomach/small intestine) include ethyl cellulose methacrylic acid ester copolymers, cellulose acetate and waxes which should also be applied in a weight ratio of from about 20:01 to about 20:6.

The following examples are provided as further teachings of the present invention so to as to better enable one skilled in the art to practice the claimed invention herein. They are for illustrative purposes only, and should not be seen as limiting the spirit and scope of the claims that follow.

Example 1

15

Ethylcellulose (400 g.), stearic acid (600 g.) and diphenhydramine hydrochloride (200 g.) were blended in a standard mixer for several minutes until a homogeneous blend was obtained. A Brabender Twin Screw Extruder was set so that the heating zones of the extruder were 80°C, 85°C, 95°C and 95°C, respectively. The size of the exit nozzle was set at 2.0 mm in diameter.

The mixture was fed into the extruder at a constant, controlled rate of approximately 5 mm/sec. and the extrudate exited directly upon a conveyor belt and into a Brabender pelletizer where the extrudate strands were chopped into uniform cylinders of approximately 2.5 mm. The pharmaceutical cylinders were then transferred to a Luwa jacketed spheronizer where they were spheronized at approximately 55-60°C at a speed of 1000 rev/min for several minutes. The uniform, ovoid shaped pellets are then cooled and collected.

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Example 2

Ethylcellulose (300 g.), stearic acid (700 g.) and diphendrdramine hydrochloride (200 g.) were again
5 homogeneously blended. The Brabender Twin Screw Extruder was set so that the four continuous heating zones were 80°C, 90°C, 95°C and 95°C, respectively. The extrudate was then cut into uniform cylindrical pellets
10 of 2.0 mm. in length and approximately 1.0 mm in diameter. Once they were fed into a Luwa jacketed spheronizer, calcium carbonate was added to minimize tackiness. The pellets were spheronized at 2000 rev./min. at approximately 60°C. for fifteen minutes in order to form generally uniform, spherical pellets. The
15 pellets were cooled and collected. The pellets were further coated using a fluidized bed coating apparatus and a sufficient amount of hydroxymethylpropyl cellulose until a pellet/coating weight ratio of 10:1 was achieved. The pellets formed thereby displayed modified release
20 characteristics.

Example 3

The same procedure was followed as in Examples 1 and
25 2 except that ethylcellulose (400 g.), stearic acid (300 g.) diphenhydramine hydrochloride (200 g.) were mixed to a homogeneous blend and to this was added on excipient, stearic alcohol (300 g.). The blend was fed to a Brabender Twin Screw Extruder whose form heating zones
30 were set at temperatures of approximately 80°C, 95°C, 95°C and 95°C, respectively.

The nozzle openings of the extruder and the pelletizer knives were set so that extrudate cylindrical
35 pellets were obtained that were 2.75 mm in length and 2.1 mm. in diameter. The exudate was fed into the pelletizer at a rate of approximately 7 mm./sec. and once cut, were

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transferred to the jacketed spheronizer which was heated to approximately 80°C. The pellets were then spheronized at approximately 2000 rev./min. for several minutes until uniform, spherical pellets were produced. During the spheronization process, magnesium trisilicate was added to minimize tackiness and prevent the tablets from sticking together. The finished pharmaceutical pellet cores were then coated with a sufficient amount of Eudragit L-30D in a fluid bed apparatus to provide enteric/sustained release pellets.

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We Claim:

1. A process for the preparation of pharmaceutical pellets comprising:
 - a) blending an active agent together with excipient materials until a homogeneous mixture is attained;
 - b) extruding said mixture under one or more temperatures so as to form a congealed mass of said mixture comprising the extrudate;
 - c) cutting the extrudate into substantially uniform cylindrical segments;
 - d) spheronizing said segments at appropriate speed and temperature to form substantially uniform, equal-sized pharmaceutical pellets and;
 - e) collecting said pharmaceutical pellets.
2. The process of claim 1 further comprising the addition of an anti-adherent during spheronization.
3. The process of claim 2 further comprising coating said pharmaceutical pellets so as to provide them immediate release characteristics.
4. The process of claim 2 further comprising coating said pharmaceutical pellets so as to provide them enteric release characteristics.
5. The process of claim 2 further comprising coating said pharmaceutical pellets so as to provide them modified release characteristics.

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6. The process of claims 3,4, or 5 wherein said active agent is selected from the group consisting of analgesics, anti-inflammatory agents, antibiotics, anti-depressants, anti-epileptics, anti-hypertensive agents, neuroleptics, anti-arrhythmics, corticosteroids lipid regulating agents, antacids, laxatives, anti-ulcer agents and mixtures thereof.
7. The process of claim 6 wherein said excipient materials are selected from the group consisting of cellulose and its derivatives, starch and starch derivatives, waxes, surfactants, lubricants, inorganic additives and mixtures thereof.
8. The process of claim 7 wherein said coating is composed of compounds selected from the group consisting of hydroxypropylmethyl cellulose, polyvinyl pyrrolidone, hydroxypropylcellulose and mixtures thereof.
9. The process of claim 7 wherein said coating is composed of compounds selected from the group consisting of cellulose acetate phthalate, methacrylic acid copolymer, cellulose acetate trimellate and mixtures thereof.
10. The process of claim 7 wherein said coating is comprised of compounds selected from the group consisting of ethylcellulose, methacrylic acid ester copolymer, cellulose acetate, waxes and mixtures thereof.
11. The process of claim 7 herein said extrusion is conducted at a temperature ranging from about 30°C to about 250°C.
12. The process of claim 11 wherein said extrusion is

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conducted at a temperature ranging from about 60°C to about 180°C.

- 5 13. The process of claim 12 wherein said extrudate segments are spheronized at a temperature of from about 30°C to about 200°C.
- 10 14. The process of claim 13 wherein said extrudate segments are spheronized at a temperature of from about 60°C to about 150°C.
- 15 15. The process of claim 14 wherein said anti-adherents are selected from the group consisting of talc, calcium carbonate, magnesium tri-silicate, kaolin and mixtures thereof.
- 20 16. A pharmaceutical pellet made by the steps comprising:
- 25 a) blending an active pharmaceutical agent with excipient materials until a homogeneous mixture is obtained;
- 30 b) extruding said mixture under one or more elevated temperatures so as to form a congealed mass comprising the extrudate;
- c) cutting the extrudate into substantially uniform cylindrical segments and;
- d) spheronizing said segments at appropriate speed and temperature to form substantially uniform, equal-sized pharmaceutical pellets,
- 35 17. The pharmaceutical pellet of claim 16 wherein said active pharmaceutical agent is selected from the group consisting of analgesics, anti-inflammatory

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- agents, antibiotics, anti-depressants, anti-epileptics, anti-hypertensive agents, neuroleptics, anti-arrhythmics, corticosteroids, lipid regulating agents, antacids, laxatives, anti-ulcer agents and mixtures thereof.
- 5
18. The pharmaceutical pellet of claim 17 wherein said excipient materials are selected from the group consisting of cellulose and its derivatives, starch and starch derivatives, waxes, surfactants, inorganic additives, lubricants and mixtures thereof.
- 10
19. The pharmaceutical pellet of claim 18 further comprising the addition of an anti-adherent during spheronization.
- 15
20. The pharmaceutical pellet of claim 19 wherein said pellet has been additionally coated so as to possess immediate drug release characteristics.
- 20
21. The pharmaceutical pellet of claim 19 wherein said pellet has been additionally coated so as to possess enteric drug release characteristics.
- 25
22. The pharmaceutical pellet of claim 19 wherein said pellet has been additionally coated to possess modified release characteristics.
- 30
23. The pharmaceutical pellet of claims 20, 21 or 22 wherein said anti-adherents are selected from the group consisting of talc, calcium carbonate, magnesium tri-silicate, kaolin and mixtures thereof.
- 35
24. The process of claim 23 wherein said coating is comprised of compounds selected from the group consisting of hydroxypropylmethyl cellulose,

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polyvinyl pyrrolidone, hydroxypropylcellulose and mixtures thereof.

- 5 25. The process of claim 23 wherein said coating is comprised of compounds selected from the group consisting of cellulose acetate phthalate, methacrylic acid copolymer, cellulose acetate trimellate and mixtures thereof.
- 10 26. The process of claim 23 wherein said coating is comprised of compounds selected from the group consisting of ethylcellulose, methacrylic acid ester copolymer, cellulose acetate, waxes and mixtures thereof.

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PCT/US 92/08160

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. 5 A61K9/16														
II. FIELDS SEARCHED <div style="text-align: center; margin-top: 10px;">Minimum Documentation Searched⁷</div> <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 5px;"> <tr> <td style="width: 25%; padding: 5px;">Classification System</td> <td style="padding: 5px;">Classification Symbols</td> </tr> <tr> <td style="padding: 5px;">Int.Cl. 5</td> <td style="padding: 5px;">A61K</td> </tr> </table> <div style="text-align: center; margin-top: 10px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched⁸</div>			Classification System	Classification Symbols	Int.Cl. 5	A61K								
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III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 5px;"> <tr> <th style="width: 10%; padding: 5px;">Category⁹</th> <th style="width: 70%; padding: 5px;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 20%; padding: 5px;">Relevant to Claims No.¹³</th> </tr> <tr> <td style="vertical-align: top; padding: 5px;">P, X</td> <td style="padding: 5px;"> EP, A, 0 465 338 (RHONE-POULENC NUTRITION ANIMALE) 8 January 1992 see page 2, line 23 - line 39 see page 2, line 52 - page 3, line 4 see page 3, line 16 - line 19 see page 3 - page 4; example 1 --- </td> <td style="vertical-align: top; padding: 5px;"> 1, 4, 7, 11-14, 16-18, 22 </td> </tr> <tr> <td style="vertical-align: top; padding: 5px;">Y</td> <td style="padding: 5px;"> EP, A, 0 204 596 (RHONE-POULENC SANTE) 10 December 1986 see column 4, line 11 - line 57 see column 5 - column 6; example 1 --- </td> <td style="vertical-align: top; padding: 5px;"> 1-27 </td> </tr> <tr> <td style="vertical-align: top; padding: 5px;">Y</td> <td style="padding: 5px;"> DE, A, 2 831 778 (GIST-BROCADES) 25 January 1979 see page 16 - page 17; example 1 --- </td> <td style="vertical-align: top; padding: 5px;"> 1, 7, 11-14, 16 </td> </tr> </table>			Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claims No. ¹³	P, X	EP, A, 0 465 338 (RHONE-POULENC NUTRITION ANIMALE) 8 January 1992 see page 2, line 23 - line 39 see page 2, line 52 - page 3, line 4 see page 3, line 16 - line 19 see page 3 - page 4; example 1 ---	1, 4, 7, 11-14, 16-18, 22	Y	EP, A, 0 204 596 (RHONE-POULENC SANTE) 10 December 1986 see column 4, line 11 - line 57 see column 5 - column 6; example 1 ---	1-27	Y	DE, A, 2 831 778 (GIST-BROCADES) 25 January 1979 see page 16 - page 17; example 1 ---	1, 7, 11-14, 16
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<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>														
IV. CERTIFICATION <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 5px;"> <tr> <td style="width: 50%; padding: 5px;"> Date of the Actual Completion of the International Search <div style="text-align: center; margin-top: 10px;">06 JANUARY 1993</div> </td> <td style="width: 50%; padding: 5px;"> Date of Mailing of this International Search Report <div style="text-align: center; margin-top: 10px;">10.02.93</div> </td> </tr> <tr> <td style="padding: 5px;"> International Searching Authority <div style="text-align: center; margin-top: 10px;">EUROPEAN PATENT OFFICE</div> </td> <td style="padding: 5px;"> Signature of Authorized Officer <div style="text-align: center; margin-top: 10px;">BOULOIS D. <i>Boulois</i></div> </td> </tr> </table>			Date of the Actual Completion of the International Search <div style="text-align: center; margin-top: 10px;">06 JANUARY 1993</div>	Date of Mailing of this International Search Report <div style="text-align: center; margin-top: 10px;">10.02.93</div>	International Searching Authority <div style="text-align: center; margin-top: 10px;">EUROPEAN PATENT OFFICE</div>	Signature of Authorized Officer <div style="text-align: center; margin-top: 10px;">BOULOIS D. <i>Boulois</i></div>								
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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	WD,A,8 303 756 (ROUSSEL-UCLAF) 10 November 1983 see page 4, line 6 - line 24 see page 5 - page 6; example 1 ---	1,4-6, 10, 16-18, 21,22,27
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